Medicinski podmladak

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Mini review article

INDICATORS OF INFLAMMATORY, MULTIORGAN IMPAIRMENT AND REDOX BIOMARKERS AND CT FINDINGS IN PATIENTS WITH COVID-19 PNEUMONIA

POKAZATELJI MARKERA INFLAMACIJE, OŠTEĆENJA ORGANA, OKSIDATIVNOG OŠTEĆENJA MAKROMOLEKULA I PROMENA NA CT TORAKSA PACIJENATA SA COVID-19 PNEUMONIJOM

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Abstract

Coronavirus disease 2019 (COVID-19) is a multi-systemic disease caused by Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2. Since the onset of the pandemic, understanding the pathophysiological mechanisms of this disease has posed a significant challenge, with the intent to determine its progression and implement appropriate treatment strategies. The heightened severity and mortality associated with SARS-CoV-2 infection can be attributed, in part, to a phenomenon known as cytokine storm. This refers to an uncontrolled systemic inflammatory response characterized by elevated proinflammatory cytokines and chemokines, leading to an overproduction of free radicals. The aforementioned cytokine storm is accompanied by the excessive generation of reactive oxygen species and affects the virus and directly damages the host's cells. Given that the SARS-CoV-2 virus primarily targets respiratory cells, pneumonia is a common manifestation of the disease. Consequently, chest multidetector computed tomography (MDCT) plays a crucial role in evaluating lung tissue inflammation, determining disease severity, making decisions regarding hospitalization, and assessing the necessity of intensive care unit treatment. Assessing the level of oxidative stress can be accomplished by measuring the products resulting from damage to lipids, proteins, and DNA - whereas the inflammatory and multiorgan impairment biomarkers can be procured from routine laboratory practice. Due to the established association of a cytokine storm with a free radical storm, it might be postulated that during the acute phase of COVID-19 pneumonia the redox biomarkers might correlate with inflammatory and multiorgan impairment biomarkers, as well as chest MDCT findings.

Keywords:
COVID-19, oxidative stress, chest CT, MDA, AOPP, 8-OHdG

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Sažetak

COVID-19 (engl. *Coronavirus disease 2019*) je multisistemska bolest koju izaziva koronavirus teškog akutnog respiratornog sindroma 2 (engl. *Severe acute respiratory syndrome coronavirus 2* - SARS-CoV-2). Od samog početka pandemije ova bolest predstavlja ogroman izazov u rasvetljavanju patofizioloških procesa koji leže u njenoj osnovi kako bi se mogao odrediti njen tok i preduzeti adekvatno lečenje. Glavni razlog za nastanak teže kliničke slike i mortaliteta povezanog sa SARS-CoV-2 infekcijom, između ostalog, uključuje citokinsku oluju, tj. nekontrolisani sistemski inflamatorni odgovor koji dovodi do povećane produkcije proinflamatornih citokina i hemokina, a za koji je pokazano da može da indukuje i povećanu produkciju slobodnih radikala. Prekomereno stvaranje reaktivnih vrsta kiseonika takođe može imati direktan destruktivan efekat na ćelije domaćina, a ne samo na virus. Pošto virus SARS-CoV-2 ima tropizam za respiratorne ćelije, česta manifestacija bolesti je pneumonija, zbog čega multidetektorska kompjuterizovana tomografija (MDCT) toraksa ima veliki značaj u cilju procene zahvaćenosti plućnog parenhima inflamacijom, ali i stratifikacije težine bolesti, odluke o eventualnoj hospitalizaciji, kao i potrebi za lečenjem u jedinici intenzivne nege. Stepen oksidativnog stresa možemo da procenimo određujući nivo produkata koji nastaju kao rezultat oštećenja lipida, proteina i DNK, dok se biomarkeri inflamatornog i multiorganskog oštećenja mogu dobiti iz rutinske laboratorijske prakse. Zbog utvrđene povezanosti citokinske oluje sa olujom slobodnih radikala, može se pretpostaviti da, tokom akutne faze COVID-19 pneumonije, pokazatelji oksidativnog oštećenja makromolekula mogu biti u korelaciji sa laboratorijskim parametrima inflamacije, biohemijskim markerima oštećenja pojedinih organa, kao i sa promenama na MDCT toraksa.

Ključne reči:
COVID-19,
oksidativni stres,
MDCT toraksa,
MDA, AOPP,
8-OHdG

Introduction

The rapid emergence of the SARS-CoV-2 virus has triggered a global pandemic with profound health implications. According to the World Health Organization, there has been a significant increase in mortality rates during this period. It is projected that the eventual mortality toll may surpass the cumulative mortality attributed to all infectious diseases witnessed in recent decades. These circumstances carry unprecedented health consequences that have not been observed previously (1).

Coronaviruses are a group of viruses classified under the *Coronaviridae* family, characterized by their possession of single-stranded RNA (2). In the case of SARS-CoV-2, the primary receptor on the surface of the host's target cells is angiotensin-converting enzyme 2 (ACE2). The virus binds to ACE2 through its receptor binding domain (RBD) (3). Upon entering the host's cells, the virus initiates the replication process, which occurs prior to detection and prevention by the immune system's mechanisms (4).

Since its inception, the disease induced by this virus has posed significant challenges in terms of diagnosing, treating, and monitoring the disease, as well as unraveling the underlying pathophysiological mechanisms that drive its progression (5). Notably, a prominent feature of COVID-19 is the presence of robust inflammation, particularly observed in individuals who have developed severe manifestations of the disease. This pronounced immune response, facilitated by a cascade of cytokines, referred to as a cytokine storm, plays a pivotal role in the pathogenesis of this illness (6).

The generation of free radicals is a non-specific response of the body to combat viral infections. Besides their direct involvement in the immune response, free radicals also function as signaling molecules that modulate the activity of immune cells and other cellular processes. In the context of an exaggerated immune reaction to COVID-19, a cascade of free radicals accompanies the cytokine storm, leading to the establishment of a detrimental cycle, where various cytotoxic effects arise due to the influence of free radicals. The oxidation of biologically essential macromolecules, including proteins, lipids, and nucleic acids, constitutes a significant component of the pathophysiological foundation underlying the origin and progression of COVID-19 (7).

Radiological diagnosis plays a pivotal role in the comprehensive management of the disease, encompassing diagnosis, treatment, and disease monitoring. Among the available imaging modalities, multidetector computerized tomography (CT) has emerged as the preferred method (8).

Inflammatory Biomarkers

Numerous studies conducted thus far have revealed that the laboratory presentation of COVID-19 can vary among patients. A common finding in individuals with COVID-19 is a decreased lymphocyte count accompanied by mild thrombocytopenia (9). For instance, a significantly lower absolute number of leukocytes, neutrophils, and lymphocytes was observed in patients with COVID-19 pneumonia upon admission (10). Additional studies investigating the cellular components of blood counts during the acute phase of COVID-19 have demonstrated that lymphopenia, observed in COVID-19 patients,

contributes to the dysregulation of immune responses, consequently leading to an exacerbated systemic inflammatory response. (11). Indeed, the presence of lymphopenia has been identified as a predictor of an unfavorable prognosis in patients with COVID-19 (12–14).

During the acute phase of the disease, increased levels of inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin have been observed. It is noteworthy to mention that while CRP has a higher diagnostic value compared to procalcitonin, measuring procalcitonin concentration can be valuable in predicting the progression of the disease (15). Notably, a significant number of patients exhibit elevated ferritin levels, and the trend of ferritin concentration closely follows that of high-sensitivity C-reactive protein (hs-CRP) concentration (16).

Following the course of the disease through seven-day intervals, Kosanović et al. have established a significant trend of increase in the absolute number of monocytes during the monitoring period (10). This finding is significant as lung macrophages play a crucial role in dampening the inflammatory response and initiating reparative processes (17). Additionally, Park et al. demonstrated that individuals experiencing pulmonary post-acute sequelae of SARS-CoV-2 infection (PACS) had elevated levels of circulating monocytes and increased activation of these cells several months after the initial infection (18).

Limited research has focused on investigating the relationship between the degree of inflammation and chest computed tomography (CT) findings in patients with COVID-19 pneumonia. Kosanović et al. highlighted the connection between acute phase reactant levels and more complex patterns of inflammation observed on thorax multidetector CT scans (10). Moreover, Carrubbi et al. demonstrated that patients with a more severe form of the disease and pronounced inflammatory changes in the lungs exhibited higher ferritin concentrations, independent of age and gender (19). What is more, Santa Cruz et al. found a positive correlation between interleukin-6 (IL-6) and C-reactive protein (CRP) levels and chest CT changes, with IL-6 showing better predictability for disease progression (20). Finally, Zhang et al. showed that the degree of lung parenchymal inflammation correlated with certain acute phase reactant values in severely ill patients compared to those with milder forms of the disease (21).

Multiorgan Impairment Biomarkers

As a viral infection, COVID-19 can result in damage to multiple organs. Various biomarkers are available to assess organ damage in individuals with COVID-19. These biomarkers primarily indicate damage to cardiac and skeletal muscle cells, hepatocytes, and kidney cells. Monitoring these biomarkers is particularly crucial for patients with more severe forms of the disease (22). Among patients with COVID-19, alterations in biomarker values associated with multiorgan impairment have been observed. These include increased activity of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) enzymes, as well as elevated concentrations of total bilirubin. Conversely, albumin levels tend to decrease. Furthermore, increased activities of creatine kinase (CK) and creatinine (Cr) have been documented. The progression of COVID-19 to a severe form, particularly in individuals with pre-existing comorbidities, leads to significant disturbances in these multiorgan impairment biomarkers (15).

It is crucial to acknowledge that the levels of these biomarkers can vary over time, and even though they may be correlated with disease severity, they may not always accurately predict the disease outcome (14). In the study conducted by Kosanović et al., significant alterations were observed in the activity of non-functional plasma enzymes, including creatine kinase, ALT, AST, and LDH, as well as changes in urea and creatinine concentrations among all patients (10). In another study by Ma et al., liver damage was more frequently observed in patients with a more severe form of COVID-19 pneumonia. However, this liver damage did not appear to harm the disease outcome (23).

A comprehensive meta-analysis, encompassing a large number of patients, revealed that individuals with a severe form of COVID-19 exhibited higher LDH activity compared to those with a milder form of the disease (24). Moreover, elevated LDH levels upon admission were found to be significantly correlated with an increased risk of developing acute respiratory distress syndrome (ARDS) and mortality (25). Additionally, a gradual decrease in LDH levels was observed within a ten-day period following admission in patients with milder forms of the disease. Consequently, LDH is considered an independent predictor, as its early decrease may be associated with a more favorable outcome (26).

Redox Biomarkers

The concept of redox homeostasis implies mechanisms that allow the body to maintain a subtle balance between the production of free radicals and their neutralization (27). In the case of SARS-CoV-2 infection, several studies have proposed that COVID-19 pathophysiology involves disrupted redox homeostasis, leading to oxidative stress that plays a significant role in the disease progression and outcome. These events are closely linked to the inflammatory processes (28). Assessment of oxidative damage can be done using routine or advanced laboratory methods, which involve measuring the concentrations of biomarkers related to oxidative damage of lipids, DNA, and proteins.

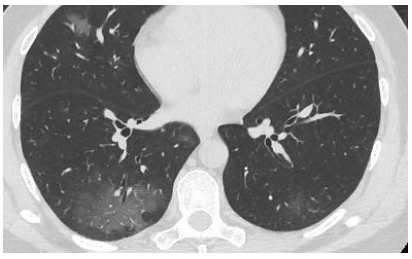
Another biomarker used to assess oxidative stress is MDA (malondialdehyde), resulting from lipid peroxidation. Monitoring MDA levels during the acute phase of COVID-19 pneumonia can provide valuable information about the extent of oxidative stress and potentially serve as a biomarker for evaluating the

severity of COVID-19 and predicting disease prognosis. In a study conducted by Mehri et al., three times higher levels of MDA were observed in the serum of patients with COVID-19 compared to a healthy control group (29). Furthermore, the study revealed that serum MDA levels were significantly elevated in patients who required intensive care unit treatment compared to those who did not (29). These findings highlight the association between oxidative stress and disease severity in COVID-19.

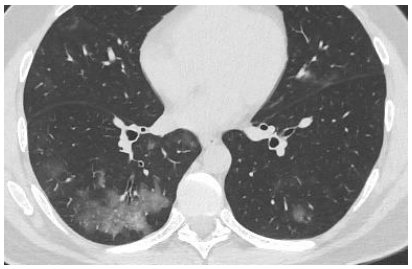
A marker that has demonstrated its effectiveness in evaluating oxidative DNA damage during the acute phase of COVID-19 is 8-OHdG (8-hydroxy-2 deoxyguanosine). Scholars like Basaran et al. found that all COVID-19 patients in their study exhibited DNA damage, with more severe cases showing more pronounced damage (30). In a study by Gülbay et al., increased concentrations of 8-OHdG were observed among patients receiving intensive care unit treatment, although no significant difference was found between patients with mild forms of the disease and the control group (31). Notably, a study conducted by Lorente et al. reported higher serum levels of oxidative DNA damage in fatal cases compared to survivors, indicating that oxidative DNA damage could serve as a predictive factor for poor outcomes (32). These findings emphasize the role of oxidative DNA damage in COVID-19 severity and prognosis.

Advanced Oxidation Protein Products (AOPP) have emerged as a commonly used marker for assessing oxidative protein damage in COVID-19 patients. Several studies have investigated the significance of protein oxidation levels in SARS-CoV-2 infections and their relationship with the course of COVID-19. Ducastel et al. found a significant association between increased AOPP concentrations and the degree of inflammation, which correlated with the severity of COVID-19, the need for intensive care treatment, and mortality (33). The results of Wybranowski et al. support these findings and clearly demonstrate that elevated AOPP concentrations are associated with inflammation severity and disease progression in patients with COVID-19 pneumonia. Moreover, this study revealed sustained elevated AOPP levels even six and twelve months after a previous infection (34). Kosanović et al. conducted research that demonstrated a highly significant change in AOPP plasma concentration values during the follow-up period among patients with COVID-19 pneumonia (10). Furthermore, the results of this study indicate a significant correlation between AOPP concentration and markers such as CRP, ferritin, and the absolute number of neutrophils on the seventh day of admission, while on the fourteenth day of admission, AOPP concentrations correlate significantly with the concentration of IL-6, ferritin, and the absolute number of monocytes (10). These findings highlight the potential utility of AOPP as a biomarker for assessing oxidative protein damage and its association with disease severity and inflammatory markers in COVID-19 patients.

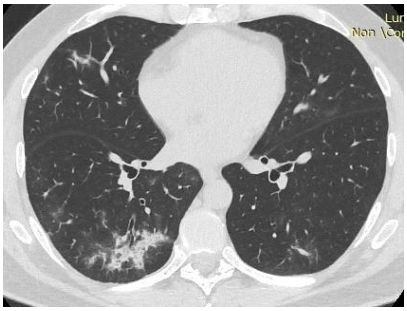
Attempts have been made to elucidate the association of impaired redox balance in COVID-19 pneumonia and inflammatory changes present in MDCT (10, 34). Although the provided results indicated some correlation between certain complex CT findings and the levels of protein and lipid redox biomarkers, no clear conclusions have been drawn. However, such findings provided grounds for postulating the role of ferroptosis in the pathogenesis and progression of the COVID-19 pneumonia (35).



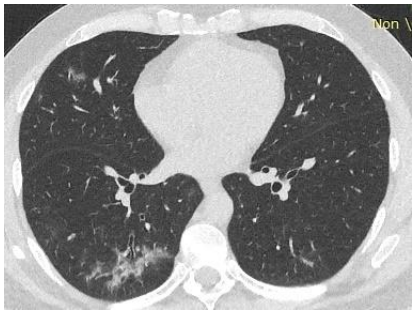
(A) Day 4 Initial phase



(B) Day 8 Progressive phase



(C) Day 13 Peak phase



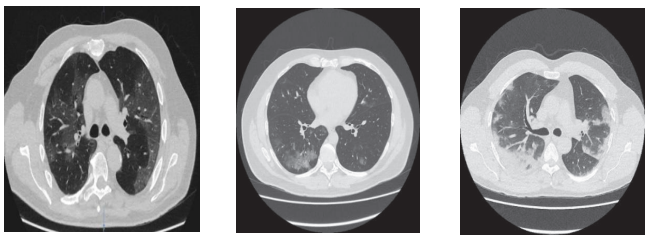
(D) Day 18 Resolution Phase

Figure 1. Examples of representative illustrations of changes on chest CT according to the stages through which COVID-19 passes (Figure A, Figure B, Figure C and Figure D); Source: Archives of Clinical Hospital Center "Dr. Dragiša Mišović - Dedinje", with the permission of the institution.

Chest CT Findings

Typical patterns seen in patients with COVID-19 pneumonia on chest CT are ground-glass opacities (GGO), consolidation, and crazy paving pattern (CP). The distribution of these patterns is bilateral and multifocal, where the changes predominantly occur in the peripheral and posterior parts of the lungs (8, 36–39). Numerous studies have shown that changes in the lung parenchyma accompany certain stages of the disease, which are also accompanied by changes that can be seen on a chest CT. A description of the four phases of the disease is provided in **figure 1**.

In the early phase of COVID-19, the most common findings on chest CT are indeed ground-glass opacities (GGO) and the crazy paving pattern (CP). These abnormalities are typically bilateral and multifocal, meaning they affect multiple lobes of the lungs. Consolidation (CON), which appears as areas of increased density, may also be present but is seen in a smaller number of patients (**figure 2**).



(A) Changes according to "ground glass" type

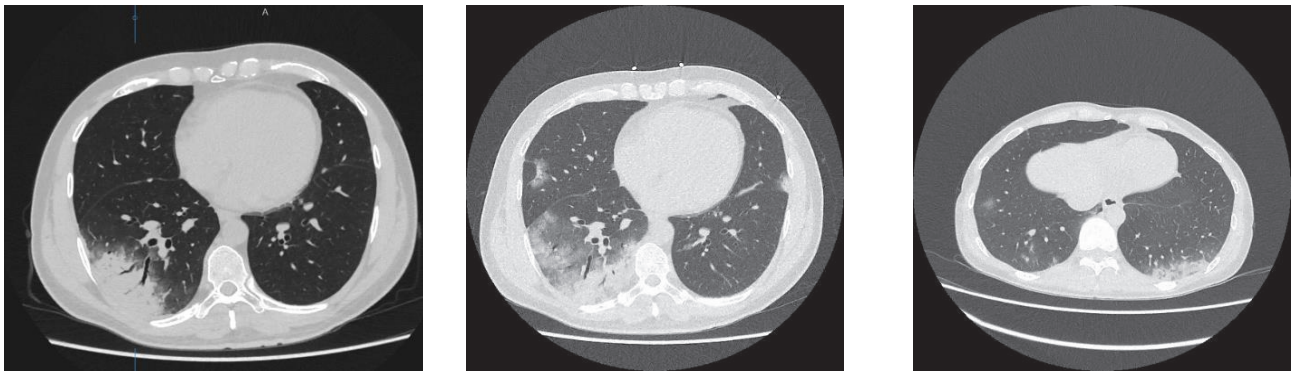
(B) Changes according to "ground glass" and "crazy paving pattern" type

(C) Changes according to "ground glass" and "crazy paving pattern" type with consolidation

Figure 2. Representative illustration of changes in the lung parenchyma on thorax CTs at admission (Figure A, Figure B and Figure C); Source: Archives of Clinical Hospital Center "Dr. Dragiša Mišović - Dedinje", with the permission of the institution.

During the progressive phase of COVID-19 pneumonia, the patterns of crazy paving (CP) and consolidation (CON) can continue to evolve. These patterns are often found in areas where ground-glass opacities (GGO) were previously observed. Disease progression in this phase may involve a significantly larger area of the lung being affected. The distribution of these changes is typically subpleural (near the surface of the lungs) and peribronchovascular (around the bronchial tubes). The lower lobes of the lungs are more frequently involved, although the changes can also diffuse and affect the entire lung parenchyma. In the peak phase of the disease, in addition to the previously mentioned CP and CON patterns, other patterns may become more prominent. These include the reversed halo sign (a central ground-glass opacity surrounded by a ring of consolidation), bronchiectasis (abnormal dilation of the bronchial tubes), and perilobular opacification (opacities around the edges of the lobes) (**figure 3**).

During the resolution phase of COVID-19 pneumonia, the time course and extent of changes in the lungs can vary depending on the severity of the previous stages. This phase is characterized by the presence of residual ground glass opacities (rGGO), residual consolidation, and fibrous bands. It refers to areas of lung tissue that still appear hazy or cloudy on imaging, indicating residual inflammation and fluid accumulation. Residual consolidation refers to areas where the lung tissue has become more solid and dense due to the presence of inflammatory exudate or fibrosis. In cases of milder forms of the disease, the resolution phase may involve a complete resolution of the existing changes, with the lung tissue returning to a normal appearance on imaging. This indicates that the inflammation has subsided, and the lung is recovering. It's important to note that the resolution phase can vary in duration and may take weeks to months for complete resolution, especially in cases where the disease has been more severe or extensive. Close monitoring and follow-up imaging may be necessary to

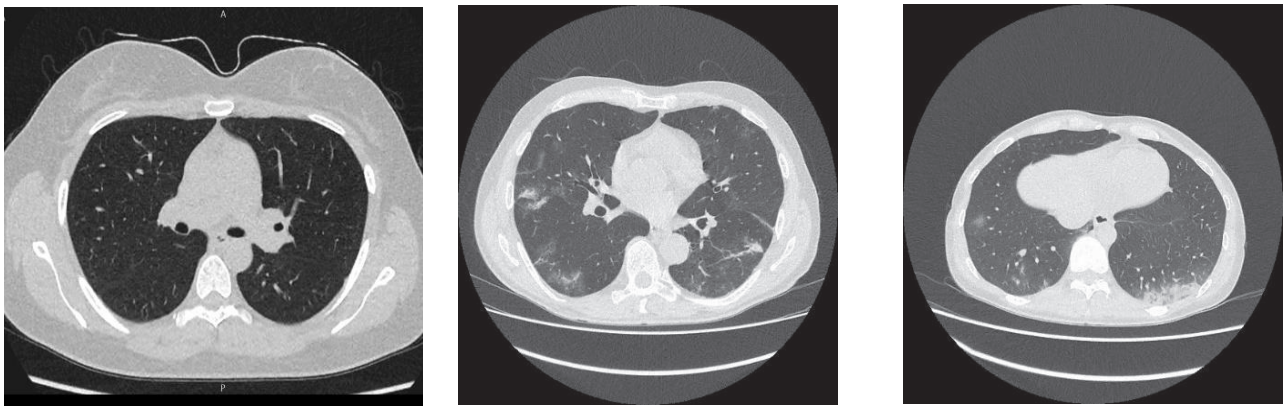


(A) Consolidation

(B) Consolidation with changes according to "ground glass" type

(C) Changes according to residual "ground glass" type

Figure 3. Representative illustration of changes in the lung parenchyma on thorax CTs on the 7th day upon admission (Figure A, Figure B and Figure C); Source: Archives of Clinical Hospital Center "Dr. Dragiša Mišović - Dedinje", with the permission of the institution.



(A) No change

(B) Changes according to residual "ground glass" type

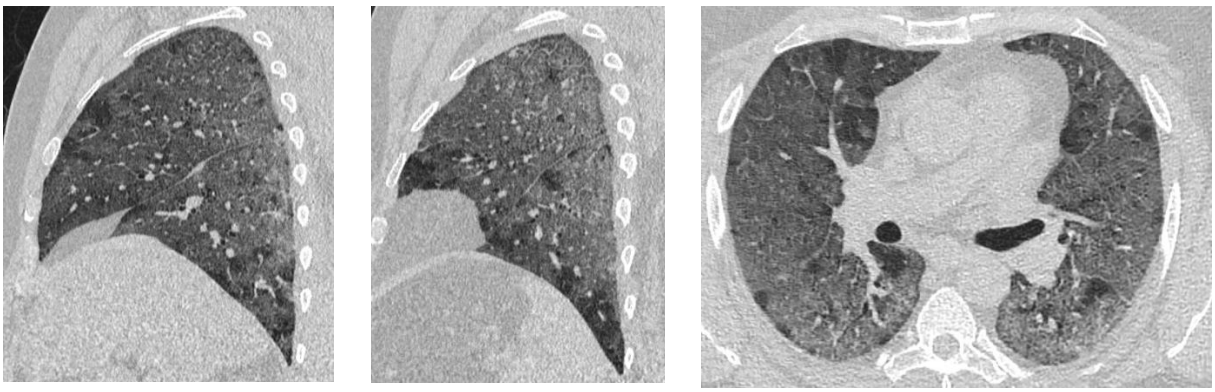
(C) Changes according to residual "ground glass" type with consolidation

Figure 4. Representative illustration of changes in the lung parenchyma on thorax CTs on the 14th day upon admission (Figure A, Figure B and Figure C); Source: Archives of Clinical Hospital Center "Dr. Dragiša Mišović - Dedinje", with the permission of the institution.

assess the progression of resolution and ensure proper healing of the lungs (**figure 4**) (40–44).

The CT disease severity score (CT SS) is a scoring system used to assess the severity of COVID-19 based on the extent of lung involvement seen on chest CT scans. The score is calculated for each lobe of the lung individually and then summed up to obtain an overall CT SS according to the following criteria: if there are no changes in the lung parenchyma the score is 0; if the lung parenchyma is affected by inflammatory changes 1 - 5%, the score is 1; if coverage is 5 - 25% the score is 2; if it is 25 - 50% the score is 3, whereby lung parenchyma coverage 50 - 75 % indicates a score of 4; and if more than 75% of the lung parenchyma is affected by inflammation, the score is 5. Overall CT SS is obtained by adding the values of the CT scores of all lobes. Therefore, the maximum possible CT SS score is 25, indicating severe involvement of the lung parenchyma (**figure 5**) (45). This scoring system allows for a standardized and quantitative assessment of the extent of lung inflammation in COVID-19 patients. It helps in evaluating the severity of the disease and monitoring the progression or regression of lung changes over time. It can also provide valuable information for clinical decision-making, prognosis estimation, and treatment monitoring in patients with COVID-19.

The study by Yazdi et al. supports the association between higher CT disease severity score (CT SS) and clinical factors such as treatment in intensive care units, prolonged hospitalization, and longer recovery periods in patients with COVID-19 pneumonia. They also found a correlation between higher CT SS and the presence of consolidation on chest CT scans (46). Furthermore, some studies have suggested that a CT SS greater than 18 can serve as a predictor of short-term mortality in COVID-19 patients. This indicates that a higher extent of lung involvement in chest CT is associated with a worse prognosis (47,48). Assessing inflammatory changes on chest CT scans has been shown to provide valuable information about the course of the disease, particularly in correlation with laboratory parameters of inflammation.



(A) Right lung (B) Left lung (C) CT SS 25 (maximum 25)

Figure 5. Representative example for determining CT severity score (CT SS) (Figure A, Figure B and Figure C); Source: Archives of Clinical Hospital Center "Dr. Dragiša Mišović - Dedinje", with the permission of the institution.

This suggests that chest CT findings can complement and enhance the understanding of disease progression and severity compared to laboratory tests alone (49). Overall, the CT disease severity score and the assessment of inflammatory changes in chest CT can help in risk stratification, treatment planning, and prognostication in patients with COVID-19 pneumonia. However, it is important to interpret these findings in conjunction with clinical assessment and other relevant factors to make informed decisions regarding patient management.

Conclusion

There is a significant role of cytokine storms and oxidative stress in the development of acute respiratory distress syndrome (ARDS) and multiorgan dysfunction in patients with COVID-19 pneumonia. The dysregulation of redox homeostasis and the resulting increased oxidative stress are important factors in the pathophysiology of the disease. The SARS-CoV-2 infection leads to the production of reactive oxygen species (ROS) and a decrease in antioxidant mechanisms, disrupting the balance of redox homeostasis and causing heightened oxidative stress. This oxidative stress can have detrimental effects on the host's antiviral response, impairing the ability to control viral replication. Additionally, the pronounced inflammation induced by the virus can further contribute to oxidative damage in various organs, leading to cell and tissue injury (7, 49). Another valuable diagnostic tool for assessing patients with COVID-19 pneumonia is MDCT. The inflammatory changes observed in the lung parenchyma of these patients correlate with the patterns seen on chest CT scans. These patterns, such as ground-glass opacities, consolidation, and crazy paving, provide insights into the extent and severity of lung involvement and can aid in the initial evaluation and follow-up of patients with COVID-19 pneumonia. By combining the information obtained from chest CT findings with other clinical and laboratory parameters, the progression of the disease can be better understood, and more informed decisions regarding patient management and treatment strategies could be made.

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